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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/801,648	03/17/2004	Hsiang-Fu Kung	V9661.0074	2232

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EXAMINER	
KELLY, ROBERT M	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/801,648	KUNG ET AL.
	Examiner	Art Unit
	Robert M. Kelly	1633

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-26,30 and 32* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23-26,30 and 32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *7/2/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's argument of 7/20/07 and amendment and argument of 7/2/07 are entered.

Claims 1-29, 27-29, 31, and 33-34 are cancelled.

Claims 23, 24-26, 30, and 32 are presently pending and considered.

Election/Restrictions

It is noted that all claimed subject matter drawn to non-elected inventions has been cancelled.

Claim Status, Cancelled Claims

In light of the cancellation of claims 1-29, 27-29, 31, and 33-34, all previous rejections and/or objections to such claims are rendered moot, and thus, are withdrawn.

Claim Objections

In light of the amendment to Claim 32, the objection to such for comprising non-elected subject matter is withdrawn.

Note: Misstated Rejection. It is noted that the Examiner accidentally did not include Claim 30 in the form paragraph of the rejection, however, it is noted that the substance of the rejection specifically recites Claim 30 (e.g., Official Action of 4/4/07, p. 7), and further the summary of the office action notes that Claim 30 is actually rejected.

Hence, it is clear that the claim was properly rejected, and was not withdrawn from prosecution.

Claim Rejections - 35 USC § 112 - enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23-26, 30 and 32 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, for reasons of record. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Response to Argument – Enablement

Applicant's argument of 7/2/07 has been fully considered but is not found persuasive.

Applicant argues that they have limited the scope of the disorders which are now treated (pp. 6-7, paragraph bridging).

Such is partly persuasive. The disorders no longer encompass such a wide range of disorders, such as Parkinson's, and hence, that basis of the rejection is withdrawn, but the other bases of the rejections directly pertaining to the disorders now claimed still apply.

Applicant argues that the claims have been amended to recite that the viral vectors comprise the promoters (p.7, paragraph 3).

Such is persuasive, and overcomes that basis of the rejection, however, if fails to overcome the other bases.

Applicant argues that dosages required for humans and other animals can be found from the experiments provided in rats (p. 7, paragraph 5).

Such is not persuasive. The dosages require experimentation, as is shown in the rejection, and further by claiming non-toxic and non-immunogenic, as shown by the rejection, such amounts specifically demonstrate that the broad claims encompass non-enabled embodiments.

Applicant argues that they have shown formation of new bone, and that the chance that the new bone would be formed and fused into the endogenous bone is high (p. 8, paragraph 1).

Such is not persuasive. The prior art cited demonstrates that it is not reasonably predictable that such fusion will occur, and nothing in the use of two vectors, where the prior art has accomplished the same would appear to overcome such. As such, as stated in the rejection, it is not reasonably predictable that this ectopic bone formation would enable treatment of these disorders.

Applicant argues that recombinant BMP-2 has been shown to be effective on healing segmental bone defects in a number of species (in pre-filing art), and that mesenchymal cells implanted in rats, regenerated and bridged bone defects 6 weeks after transplant (in post-filing art) (p. 8, paragraph 2).

Such is not persuasive. First, with regard to the use of the protein, versus a vector, the Examiner has shown that the use of protein for these disorders is not reasonably predictive of therapy with vectors, as is shown in the art (e.g., Official Action of 4/4/07, pp. 15-16). Second,

with regard to the post-filing art, such appears to be limited to treating age related recovery of bone defects, with MSCs, which is a much smaller range of disorders and cell types, which is already also discussed in the previous rejections (e.g., Id., pp. 15-16, paragraph bridging). Given what has been shown, it is still clear that such is not enabling of the invention. To wit, Applicant's invention appears to be the use of the combination of vectors to treat these diseases, as their examples only differ from the prior art by the combination of vectors. Hence, the Argument to enablement is that the vector combination transforms better, and thus must cause bone fusion where it was not previously caused. However, the cited post-filing art does not use the combination of vectors, but only an adenoviral vector (Yue, et al. (2005) Calcified Tissue International, 77: 395-403, e.g., p. 396, col. 2, paragraph 3). Moreover, it appears that the important reason that this post-filing Art works is not the vector which is used, but instead, the cell type (e.g., Id., pp. 400-401), which allows for compensation of the lowered amounts of MSC in aged rats, thereby allowing therapy, and further, that it all depends on a series of other unknown factors which are affected in aged animals (e.g., I.d., p. 395, last paragraph). Hence, such therapy must also be related to aged animals specifically, as young animals do not have these problems. Moreover, using the ex vivo therapy of Yue ensures enough cells are transformed, which is not the case in Applicant's method, where no transformation of MSCs ex vivo is required. Still further, as stated previously, Alden demonstrates that direct administration of adenoviral vectors to the junction fails to form fused new bone (e.g., Official Action of 4/4/07, pp. 15-16). Still further, the claims do not even require MSCs to be transformed, but instead skeletal muscle cells must be transformed. Lastly, it is simply not understood in the Art how one bone can heal another. I.e., bones are not understood in the Art to heal one and other, and hence,

Applicant's separately formed ectopic bone would not be reasonably predicted to heal a broken bone, especially since it had not been shown in the Art which did the same transformation of muscle tissue and ectopic bone formation, and further the demonstration in the Art of lack of fusion. Hence, at the time of invention, and even, the Artisan would not find Applicants claims to be predicted to successfully treat the range of disorders, via the breadth of method steps encompassed, for reasons of record.

Applicant argues that more post-filing art to Gafni, et al. (2004) Mol Ther, 9(4): 587-95 demonstrates treatment with AAV vectors expressing BMP-2 demonstrates induction and regulation of bone repair in mice, and bootstrapping on the other post-filing art of Yue (ABOVE) demonstrates enablement of the invention (p. 8, paragraph 3).

Such is not persuasive. Gafni only teaches ectopic bone formation and therefore is also subject to the same limitations as the prior art teachings. Further, bootstrapping onto Yue appears to be incorrect, as Yue uses specific vector, construct, and cell type in a specific form of disease. Given the rejection's substance, the Artisan would still not find the claims enabled.

Applicant argues that Moutsatsos, et al. (2001) Molecular Therapy, 3(4): 449-61 teaches that the invention is enabling of the present invention, as the bone fused (pp. 8-9, paragraph bridging).

Such is not persuasive. Moutsatsos is essentially the same as Yue, but uses a single vector. Hence, the same arguments apply (e.g., the use of MSC cells and ex vivo therapy and the use of old animals).

Applicant argues that the Turgeman, et al. (2001) Journal of Gene Medicine, 3: 240-51 is enabling of the invention (p. 9, paragraph 2).

Such is not persuasive. Turgeman follows a review of the use of mesenchymal stem cells to affect treatment, not direct administrations to the site of the damage. Hence, for the same reasoning as in Moutsatsos and Yue, this references fails to enable the invention claimed.

Applicant argues that Chen, et al. (2003) Gene Therapy, 10: 1345-53 is enabling of the invention.

Such is not persuasive. Chen teaches orthotopic bone formation, and the Art has already shown that such direct injections of similar vector at the site of defect will not reasonably predict therapy, due to absence of bone fusion, and the other reasoning provided in the Official Action of 4/4/07. (I.e., why is it that prior art demonstrates that the direct injection of similar vectors did not allow fusion?)

Applicant argues that their demonstrations by way of Example overcome the enablement (p. 9, last paragraph).

Such is not persuasive. As has been argued in the Official Action of 4/4/07, such is not reasonably predicted to cause the newly formed bone to fuse.

Applicant takes issue with the Examiner's statement of inappropriate bone-like structure formation (p. 10, paragraph 3).

Such is not persuasive. Call it a bird if you want, it is ectopic bone formation, and as it is not located at the bone, but within muscle, it is inappropriate as it is not the natural location. Moreover, the term bone-like structure is used because it is a bone structure, but is not normal bone. However, the Examiner will in the future try to remember to call it ectopic bone formation.

Applicant argues that the ectopic bone formation is in fact useful for healing bone lesions or repairing segmental defects (p. 10, paragraph 3).

Such is not persuasive. The utility is not being rejected. However, it is not reasonably predicted to be successful for the reasons previously given.

Applicant argues that they can target the tissue, as they used an AAV vector which was previously stated may not transfect the tissue of interest (pp. 10-11).

Such is not persuasive. Applicant has not demonstrated how every vector is reasonably predicted, even when AAV-2 is demonstrated, as it has been shown the AAV vectors do not reasonably predict each other by the same arguments the Applicant is discussing.

Applicant argues that the Examiner's statement that the majority of gene therapy with BMPs involves regeneration of bone defects, and is not reasonably predictive of any disorder is incorrect, supporting it with art involving bone (p. 11, paragraph 3-last paragraph).

Such is a moot point. Applicant's claims are now limited to bone disorders and regeneration of new bone.

Applicant continues the arguments with regard to the breadth of disorders (p. 12).

Such is a moot point. Applicant's claims are now limited to bone disorders and regeneration of new bone.

As a final statement, to the make the very core of the rejection clear, it is noted that the prior art demonstrates treatment of muscle with viral vectors to express BMP-2 and subsequent ectopic bone formation, as well as direct administration to sites near the break (e.g., Official Action of 4/4/07, pp. 15-16). However, the prior art similarly fails to demonstrate that such results in fusion, and in fact demonstrates that no fusion takes place (Id.), and hence, no therapy

can take place. The Examiner simply fails to understand how a combination of vectors overcomes the problem. Explanation of why the delivery vehicle makes a big difference to the expressed protein's effects would be very helpful in getting Applicant a patent, although this is not a requirement for information.

Note

The claims examined are free of the Art of record.

While the Art recognized that Adenoviral vectors could be used to produce ectopic bone in muscle (e.g., Alden, et al. (1999) Human Gene Therapy, 10: 2245-53, ABSTRACT), the Art also recognized that these vectors produced immune responses which could preclude production of such bone (e.g., Id.). Moreover, while the Art already recognized the ability of adenoviral vectors to provide for increased AAV transfection efficiency in muscle (Malik, et al. (2000) J. Virology, 74(8): 3555-65, ABSTRACT), and the Art also recognized the ability of AAV to transform, *inter alia*, muscle (e.g., Abadie, et al. (2002) Gene Therapy, 9: 1037-43, ABSTRACT), the Art does not teach or fairly suggest the cotransformation of cells to produce bone, via the claimed dual-vector system. Such is because the Art in general recognized that immune response to the adenoviral vectors would likely preclude bone formation, as taught in the Art. Further, as therapy is required, the Artisan would simply not predict it to be efficacious.

Further, to support such analysis, the first art to demonstrate this ability to work in immunocompetent animals is the inventor's art: Chen, et al. (2004) Biochem. Biophys. Res. Commun., 317(3): 675-81.

However, as noted above, the claims are not enabled for a patentable use.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert M. Kelly, Art Unit 1633, whose telephone number is (571) 272-0729. The examiner can normally be reached on M-F, 9:00am-5:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach can be reached on (571) 272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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